Molecular detection of pulmonary oxygen toxicity using exhaled breath analysis after hyperbaric hyperoxic exposure.

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Primary Objective: To study the differences between EB post oxygen-dive, post air-dive (control), dry-dive (recompression chamber) and pre-dive (baseline).1. Will an exposure to a PO2 of 190 kPa (100% oxygen at 9 msw) during 60 minutes in an...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON44355

Source
ToetsingOnline

Brief title
Hyperbaric Oxygen and Pulmonary Toxicity

Condition

- Other condition
- Lower respiratory tract disorders (excl obstruction and infection)

Synonym
chronic oxygen poisoning, late onset oxygen poisoning.

Health condition

beroepsmatige blootstelling aan fysische factoren

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Koninklijke Marine

Intervention

Keyword: Diving, Hyperbaric Oxygen, Volatile Organic Compounds

Outcome measures

Primary outcome

1. Will an exposure to a PO2 of 190 kPa (100% oxygen at 9 msw) during 60

minutes in an immersed setting lead to changes in EB compared a PO2 of 40 kPa

(21% oxygen at 9 msw)?

2. Will a repetitive exposure to a PO2 of 250 kPa (100% oxygen at 15 msw,

similar to HBOT) during 90 minutes in a dry setting lead to changes in EB?

Secondary outcome

a. Difference in EB measured by SpinoNose or GCMS.

b. Time interval post-dive which gives the best markers for POT.

Study description

Background summary

Exposure to hyperoxia is common in military oxygen diving and in hyperbaric oxygen therapy (HBOT). Breathing oxygen at a partial pressure (PO2) of more than 50 kPa for a longer duration can lead to pulmonary oxygen toxicity (POT). (Klein 1990, Miller 1981) The most mentioned changes which can be found are atelectasis, interstitial oedema and inflammation. (Sackner 1975) These changes are reversible. (Winter 1972) However, when the administration of oxygen is continued, this will eventually lead to irreversible lung fibrosis. (van Ooij 2013, Kapanci 1972)

The current standard for determining POT in diving and hyperbaric medicine, is a decrease in vital capacity (VC). (Clark 1970) Bardin & Lambertsen related the decrease in VC to the PO2 and time exposed to oxygen and introduced the unit of pulmonary toxicity dose (UPTD). (Bardin 1970) To cope with the wide range of inter- and intrapersonal variability, the limits of acceptable oxygen exposure are based on median decreases in VC. For instance; 450 UPTD gives a 2% decrease in VC in 50% of the cases. The decrease in VC was derived from dry-dives (in a recompression chamber), not from actual hyperbaric oxygen in an immersed setting. At the time of publication, the authors recognized the limitations of the model and suggested that more advanced research techniques would probably increase the validity of the UPTD model.

Recent publications indicate that more advanced parameters such as diffusion capacity of carbon monoxide (DLCO) and nitric oxide (DLNO), could more accurately determine POT. (van Ooij 2014) However, these measurements are quite difficult to perform and require specialised equipment. Therefore, these methods cannot be used by clinicians or divers as a measurement of POT in an outward setting. In combination with the recent findings that immersion affects the rate at which POT develops and the high intra- and interpersonal variance, the diving industry and the field of hyperbaric medicine needs a new and valid model which allows correction for individual susceptibility.

In an earlier study we found volatile organic compounds (VOCs) detected in a single exhaled breath (EB) four hours after a hyperbaric exposure (with Gas Chromatography Mass Spectrometry [GCMS] analysis). (van Ooij 2014) The conclusion if this study was that more accurate EB measurement should be performed less than four hours post-dive, however the exact moment is unknown. Also, the GCMS-analysis requires an external laboratory. Therefore, the traditional method analysing EB does not meet the requirements of point-of-care testing.

With the recent development of the SpiroNose® by the department of respiratory medicine in the Academic Medical Center a highly advanced technique became available to overcome these difficulties. The SpiroNose allows analysis of EB and compare it to an online database. However, no research has been conducted to validate VOCs detected by the SpiroNose are just as valid as GCMS to detect POT after (immersed) hyperbaric oxygen exposure.

Our hypothesis is that VOCs detected with the SpiroNose in a single exhaled breath are just as valid as DLNO/CO and are a patient-friendly and easy to use method to detect POT after hyperbaric oxygen exposure.

Study objective

Primary Objective:
To study the differences between EB post oxygen-dive, post air-dive (control), dry-dive (recompression chamber) and pre-dive (baseline).

1. Will an exposure to a PO2 of 190 kPa (100% oxygen at 9 msw) during 60 minutes in an immersed setting lead to changes in EB compared a PO2 of 40 kPa (21% oxygen at 9 msw)?
2. Will a repetitive exposure to a PO2 of 250 kPa (100% oxygen at 15 msw, similar to HBOT) during 90 minutes in a dry setting lead to changes in EB?

Secondary Objective(s):
1. Is the SpiroNose just as sensitive in detecting VOCs in EB associated with POT as GCMS?
2. Which time-interval post-dive give the most reliable result to detect POT?

Study design

Experiment I * *Wet dives*
This is a randomized cross-over trial which has three measuring days per subject. All measurements and experiments will be performed at the Royal Netherlands Navy Diving Medical Center at the Naval harbour in Den Helder, the Netherlands.

Study day one (Monday): baseline measurements in which we measure DLNO/CO and EB without being exposed to either oxygen or pressure in the preceding twenty-four hours. These baseline measurements will take place at least 48 hours before study day two.
Study day two (Thursday): the subject will make a dive to nine meters during sixty minutes in which he either breathes 100% oxygen (active exposure) or air (control, PO2 of 0,40 kPa) in random order. Once pre-dive and five times post-dive EB will be measured (*, 1, 2, 3 and 4 hours after exposure). DLNO/CO will be measured once at four hours post-dive. A sample of the inspired and ambient air will be taken for reference purposes.
Study day three (Thursday +1 week): this day is analogous to day two, but the subjects will breathe oxygen if they breathed air on the previous dive and vice versa. Measurements will be the same. This day will be at least one week after the previous dive to ensure all physiological parameters have been normalised.

Experiment II * *Dry dives*
This is a prospective cohort study which has seven measuring days per subject.

Study day one (Friday): baseline measurements in which we measure DLNO/CO and EB without being exposed to either oxygen or pressure in the preceding twenty-four hours. These baseline measurements will take place at least 48 hours before day two.
Study day two (Monday): Measurement of EB pre-dive. Afterwards the subject will make a dive to fifteen meters for ninety minutes in a hyperbaric chamber. In the four hours post-dive we will measure DLNO/CO once and EB three times (*, 2 and 4 hours after exposure).
Study day three (Tuesday): As day two.

Study day four (Wednesday): As day two.
Study day five (Thursday): As day two.
Study day six (Friday): As day two.
Study day seven (Monday): After two days of non-diving (comparable to regular hyperbaric oxygen treatment schedules). Exposure and measurements similar to day two.

Study burden and risks

Benefits: For military oxygen diving, as well as hyperbaric oxygen treatment, it is of vital importance to know at which level and duration (hyperbaric) oxygen can be breathed before it will lead to POT. In addition, with this research, we hope to be able to develop a *bed-side* point of care measurement to help divers and clinicians determine safe limits for hyperbaric oxygen therapy.

Risk assessment:
Decompression sickness: Any well performed in-water dive has some risk of DCS. The risk of DCS associated with the wet dive (60 minutes at 9 msw with compressed air) can be considered as very small (0.1%). The dry dive has no risk for DCS, because the subjects only breath oxygen.
Oxygen toxicity: There is a risk for both cerebral as well as pulmonary toxicity. The latter is subject of this study. The risk or cerebral oxygen toxicity during wet dives is about 4.7% as determined by Arieli and Butler.16, 17 This estimation is based on oxygen divers who are subjected to physical exertion. As our subjects will not perform any exercise we expect the risk of cerebral oxygen toxicity to be less than 4.7%. In 85 similar wet exposures in previous experiments we had no cases of cerebral oxygen toxicity. In dry dives (recompression chamber) this risk is even lower. Cases of cerebral oxygen toxicity are very rare, with incidences of 1 in 40.000 exposures not being uncommon.18,19
If nevertheless a convulsion occurs the proper action will be taken according to *Noodplan Neurologische Zuurstof Vergiftiging* (see section K6). Overall, we think the burden of these wet and dry dives can be considered low, and less than an oxygen dive in *open water* which is part of their regular work.
Barotrauma: Hyperbaric exposure requires equalisation of the middle-ear during ascends and descents to avoid tympanic membrane ruptures. All subjects are medically evaluated according to standards of the European Diving Technology Committee (EDTC), which includes evaluation of the ability to equalize.20 Additionally, all subjects trained and certified in diving or recompression procedures. Finally, ascents and descents in both experiments are artificially, with the possibility to temporarily halt the change of depth to give the subject more time to equalize. We feel this risk is negligible.
Fire hazard: Although fire in recompression chambers are extremely rare, hyperoxic conditions increase the risk of fire when combined with high temperature and fuel. To avoid any contamination (which could act as fuel) all material exposed to 100% oxygen are *oxy clean* and regularly maintained

according to both international and Dutch standards. Oxygen is administered to subjects via a breathing apparatus (wet experiments) or breathing mask (dry experiments). To ensure no oxygen is leaking, the recompression chamber is fitted with oxygen monitoring sensors. If ambient oxygen levels rise above 23% the oxygen supply is limited and the chamber starts *flushing* oxygen to the exterior. We are confident this risk is properly addressed.

Group relatedness:
Oxygen diving is only possible with adequate training and material. Navy divers are the only group in the Netherlands who are trained and certified to work with this equipment. As oxygen diving is part of their daily work, the divers will benefit of all research being conducted to increase the safety of oxygen diving.
For the dry dives, recompression personnel is medically evaluated and trained to recognize any dangers associated with hyperbaric exposure. This training consists of four weeks of education and hands-on experience. Because the Ministry of Defence considers participation of this study as *regular work*, all safety and certification standards apply. We consider it an disproportionate burden to use untrained volunteers who require 4 weeks of training before being able to participate in this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Adults
- Non-smoking
- Fit to dive according to the European Diving Technology Committee (EDTC) standards. (includes lung function tests such as DLCO % reference ERS/ATS > 70%)
- Certified Navy Divers (only applicable to wet-dives)
- Certified hyperbaric nurses and physicians (only applicable to dry-dives)

Exclusion criteria

- If one on the inclusion criteria is not met
- Recent lower respiratory tract infection and/or flue
- Daily use of alcoholic beverages

Study design

Design

Study type:	Observational non invasive
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-01-2018
Enrollment:	40

Type:	Actual

Ethics review

Approved WMO Date:	02-11-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 22684
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL61779.018.17
OMON	NL-OMON22684